Meredith. Does the committee have questions for Dr. Meredith before the FDA?

(No response.)

DR. TEMPLETON-SOMERS: Is Louise Peltier or anybody else from Guilford Pharmaceuticals here? I'd like to talk to you please. I'll be outside in the hall.

DR. NERENSTONE: The next part of our morning is the FDA presentation. Dr. Bishop.

MR. OHYE: Excuse me.

DR. NERENSTONE: I'm sorry. Mr. Ohye.

MR. OHYE: I don't have a question for Dr. Meredith, but I have a small request on behalf of the industry since I'm their industry rep.

If you've had time to assemble a formal bibliography, I would ask you to submit the bibliography to the Executive Secretary so that I can obtain same for distribution to interested parties in the industry.

DR. NERENSTONE: You mean a bibliography from Dr. Meredith's talk.

MR. OHYE: Yes, Dr. Meredith's.

DR. BISHOP: Dr. Nerenstone, members of the committee, once again good morning. I'm sure many of you find it very difficult to focus on these presentations in view of today's news. I will try to keep my remarks brief and to the point.

Over the next 30 minutes, I will focus on the most relevant efficacy and safety study results from the studies that were presented in the biologic license application for Zevalin. In part, this is because our time is limited but also because we do agree with the analyses that were performed on the primary and secondary efficacy endpoints that were presented to you by IDEC this morning. So, I will not try to duplicate this morning's presentation but again only focus on those relevant study results that will be salient to this morning's discussion and the questions to the committee.

First, the regulatory history. The results of five clinical studies were submitted to the agency in support of the proposed biologic license application. Very briefly, to remind everybody what the proposed indication is, Zevalin is being proposed for the treatment of patients with relapsed or refractory low-grade, follicular, or CD20 transformed B-cell non-Hodgkin's lymphomas and for the treatment of patients with Rituxan-refractory follicular non-Hodgkin's lymphomas.

The IND was submitted in 1992 and presented here on this slide are the dates that the five clinical studies were launched. Please note that the 106-04 study and 106-06 study, which are the two phase III pivotal studies, were initiated in 1998. The 106-98 study, which

is the open access trial, the study that is currently ongoing, was initiated in December of 1999.

Fast track designation was granted in June of 2000. The BLA was received by the agency in November of 2000. Our first action was in May of 2001, at which point we issued a complete review letter to the company.

Two months later, the company responded, and this triggered the class 2 response initiating another 6-month clock, and the next action date is January 8, 2002.

First, the efficacy results. The Zevalin BLA contains two major studies: one major controlled efficacy study and one supportive trial in the refractory setting.

First the efficacy study, study 106-04. This study was a randomized study having an active control, rituximab. Subjects enrolled in the study were stratified by histology, IWF A's, the folliculars, and then the transformed. The primary efficacy endpoint was superior overall response rate as defined in the protocol and as evaluated by an independent group, the LEXCOR group. This LEXCOR group was blinded to the study assignments.

The overall response rate for the study 106-04, which is the primary efficacy endpoint, was achieved in this trial. Zevalin had a response rate of 73 percent; rituximab, 47 percent; with a p value, a Cochran-Mantel-Haenszel test, stratified by histology, p value of .002.

Looking at subgroup analyses for overall response rate in this study, what we have learned is that few subjects with IWF A histology or transformed histology were enrolled in either the Zevalin arm with 9 subjects each for these categories and 8 subjects for the rituximab with IWF A's, 4 subjects with the transformed in the rituximab arm for the transformed.

Represented here are the number of individuals that had overall response rates with the corresponding percentage. What we learned is that follicular subjects, which are the majority of the subjects that were enrolled in this trial, indeed had a response rate of 76 percent, 42 responders, in the Zevalin arm, as compared with 47 percent, or 27 individuals, in the rituximab arm.

In the IWF A group, 6 of 9 subjects were responders, representing 67 percent of the individuals, and this was compared to 3 out of 8 individuals in the IWF A categories in the rituximab arm.

For the transformed, only 5 out of 9, or 56 percent, were responders in the Zevalin group versus 3 out of 4, or 75 percent, in the rituximab group.

The median duration of response for all responders, 53 subjects in the Zevalin versus 33 in the rituximab, was 14.2 months for the Zevalin-treated subjects versus 12.1 months in the rituximab-treated subjects.

Within this group, 25 individuals, or 47 percent, were censored. 23 of these individuals are ongoing responders. 1 individual has been lost to follow-up, and 1 individual has expired. Similarly, 42 percent of the subjects in the rituximab arm are censored, and some of these individuals being ongoing responders.

If we look at duration of response and break this down by subgroup analysis, what we find is for the IWF A's the median duration of response was 9.8 months for the Zevalin-treated subjects. Because 67 percent of the individuals are ongoing responders in the rituximab, a median is not provided.

For the follicular subjects, the median duration of response was 18.5 versus 12.1.

And for the transformed individuals, the mediation duration in the limited number of subjects, 5, was 6.8 months and in the rituximab, 11.7 months.

Now shifting to the supportive trial, the trial 106-06, which was a nonrandomized trial in the rituximab-refractory follicular, B-cell non-Hodgkin's lymphoma. There the primary efficacy endpoint was overall response rate, again as evaluated by the LEXCOR group. The LEXCOR group was again blinded to the investigator's assessment of response.

In this patient population, a prospectively

agreed upon overall response rate target of 35 percent and a duration of response comparable to prior rituximab would have been considered acceptable evidence of activity.

The primary efficacy analysis revealed an overall response rate, again protocol-defined response criteria, by the LEXCOR evaluation group, for the entire study population of 59 percent.

Now, 2 individuals within the study population did not meet protocol definition of follicular histology, and I have presented here the results for those 52 individuals that did meet the protocol-defined follicular group. In these individuals, the response rate was 58 percent. Because those 2 individuals really do not affect subsequent analysis, I am going to present to you results that include all 54 subjects.

The duration of response for the Zevalin-treated individuals, 32 responders, was 7.7 months as compared to their prior rituximab therapy. So, this is the median for the entire group. Looking at the median response for all 17 individuals who had a documented, although short, time to disease progression, the median was 4.0 months. This compares to the median for Zevalin of 7.7 months. This was the protocol-defined analysis that would have compared the duration of response of Zevalin to the rituximab.

During the review cycle of the material that was submitted in support of the license application, the FDA asked IDEC to perform an additional analysis looking at duration of response for the Zevalin therapy compared to the prior rituximab therapy, using each individual as their own control. Again, as was presented this morning, therapy was considered to be favorable towards Zevalin if the duration of response to Zevalin was at least, in our analysis, 1 month. The morning's data was at least 3 months longer. Again, the same thing with the rituximab. The alternative would be true, that if duration of response to rituximab was at least 1 month longer than Zevalin, the therapy would have been considered to favor the rituximab.

Looking at this analysis, what we find is 54 percent of the subjects would have been considered to have a duration of response that would favor the Zevalin therapy as contrasted to the 9 percent of the individuals whose duration of response would have been considered to favor the rituximab therapy.

In general, Zevalin therapy has, we believe, demonstrable and durable antitumor activity in the follicular subjects. However, there is limited data in the IWF A's and in the transformed subjects that would preclude, in our opinion, definitive conclusions. And we seek the committee's advice in terms of how they see those

two subgroups fitting in in terms of Zevalin therapy.

Now, turning to safety, the dominant safety concern with Zevalin therapy probably relates to the observed rate of cytopenias. So, let me first begin by reviewing for you the hematologic toxicities.

Represented here are the grade 3/4 neutropenias and the grade 4 neutropenias. Grade 3 neutropenia is an ANC of equal to or below 1,000. Grade 4 is an ANC of 500 or below.

What we have done is looked at the first 90 days following initiation of therapy. There 214 subjects out of the entire integrated safety analysis, or 392 subjects, representing 55 percent of the individuals, had a grade 3/4 neutropenia. The median duration of this grade 3/4 neutropenia was 25 days. Please note that the range is wide. Approximately 3 percent of the individuals included in this group did not have documented neutrophilic recovery. Now, some of those individuals had confounding factors such as going on to additional therapies.

Similarly for thrombocytopenia or platelets, 57 percent of the study population had grade 3/4 thrombocytopenia and the median duration of the 3/4 thrombocytopenia was 27 days. Again, let me emphasize that the range is wide and the plus sign here represents that some individuals, approximately 9 percent of the study

population, did not have documented platelet recovery or back to baseline. Again, some of these individuals had confounding factors such as going on to additional therapy.

Graphically the data is represented in this slide. Time 0 is the time at which Zevalin therapy was administered. What we have seen here is a predictable decline in neutrophilic count at approximately 30 days from the onset of therapy. This decline was durable for approximately 3 to 4 weeks prior to seeing a recovery. Some individuals have protracted recoveries and some individuals, as I have mentioned, did not have documented recovery, although this represented a small percentage of the population.

Putting this into context with additional effects of Zevalin therapy on the immune system, all subjects had B-cell depletion, and as was presented this morning, the median time to baseline recovery was approximately 6 months. There was a transient IgM decline which also went back to baseline within 6 months, and IgG and IgA remained normal. The reason I present this slide is, number one, to emphasize that this is similar to the profile that we see with rituximab alone and also to put it into context of the neutropenias that we see and then the incidence of infections.

114 out of the 358 data set, looking at

infection, or 32 percent of the population, had a total of 183 events. 8 percent of these individuals had grade 3 or 4 events. Represented graphically on this slide is the percentage of subjects that had at least one of those events. So, looking at bacterial for all subjects, 54 percent of individuals had at least one bacterial infection, 15 percent viral, 11 fungal. In 67, the infection was not otherwise specified.

Looking at the breakdown according to NCI CTC grade for severity, the majority of the infections were grade 1/2's with a minority of the subjects having grade 3 and 4, again 8 percent of those subjects having grade 3 and 4.

Now, shifting to thrombocytopenia, 224 individuals, or 57 percent of the population, had documented grade 3/4 thrombocytopenia, again a predictable course where we see a rapid decline at approximately day 30 and a sustained thrombocytopenia for approximately 3 to 4 weeks prior to seeing recovery. There is, again, a number of individuals that have protracted thrombocytopenias and a small percentage, approximately 9 percent, again having a documented recovery back to baseline.

Looking at the study 106-05, which was introduced this morning in Dr. White's presentation, which included individuals with a baseline platelet level that

was below 150 but above 100, what we learned is that when individuals have already a low baseline platelet at the time of receiving Zevalin therapy, a higher number of these individuals, or 87 percent of them, will incur grade 3/4 thrombocytopenia, again with the same predictable course where we see by day 30 a decline and then approximately a 3 to 4 weeks' duration of thrombocytopenia prior to recovery.

I have scaled this axis up to 210 days to emphasize that a number of these individuals can have protracted thrombocytopenia, this representing approximately 12 percent of the population. As was pointed out this morning, Dr. White indicated that a number of dots here would be missing because, as per protocol, once somebody had recovered from their hematologic toxicity, it was no longer required to continue to monitoring these individuals.

Putting this into the context of incidence of bleeding, 18 percent of the individuals enrolled had at least one bleeding event. 7 of these subjects had a total of 12 grade 3/4 events. Let me cover those 12 events for you.

2 individuals had intracranial bleed that resulted in death. One of those individuals with intracranial bleed also had a vaginal bleed and ecchymosis that was at least grade 3. 5 subjects had gastrointestinal

bleeding. Of these, 4 of them were documented as GI bleed, 1 of them hematemesis, and 3 of them melenas. One of those subjects, 1 of the 5, had a GI bleed, hematemesis, and melena occurring during the same episode.

IDEC has performed some exploratory analyses looking at cytopenias and potential risk factors predictive of cytopenias. Represented here are some of the results of those exploratory analyses. It appears that baseline bone marrow involvement, the number of prior regimens, especially when fludarabine was used, and baseline platelet level would all be predictive of grade 3/4 hematologic toxicities.

Now, shifting over to the non-cytopenic adverse events, represented here in this table are the most common adverse events that were documented in subjects enrolled in all of the studies submitted in support of the BLA. Asthenia was the predominant adverse event, followed by nausea, infections, chills, fever, abdominal pain, dyspnea, headache, increased cough, and pain. There were other nonhematologic adverse events that are not listed here, but all of them were below 15 percent.

Please note that the incidence of grade 3/4 nonhematologic adverse events was, for the most part, low in the study population. Probably the highest number was with infections, representing approximately 8 percent of

all subjects. There were 3 percent of individuals who had grade 3 asthenia, fever, and abdominal pain. 2 percent of the individuals had dyspnea. All the other nonhematologic adverse events that are not listed here either had no events that were grade 3/4's or less than 1 percent of the subjects had events that were grade 3/4's.

Looking at the comparative study, the 106-04 study comparing Zevalin therapy to the rituximab therapy, portrayed here in the bar graph are the most common nonhematologic adverse events for these two arms. Notable are asthenia and nausea, long with infections, pain and abdominal pain, where were more commonly seen in the Zevalin therapy. Other common adverse events portrayed here are chills, fever, and headaches.

What I have done in this bar graph is highlight for you some of the notable adverse events in terms of having a numeric difference between the two study arms. Increased cough, dizziness, dyspnea, peripheral edema, arthralgia, anorexia, anxiety, and ecchymosis were more common in the Zevalin-treated subjects. Please note that the majority of these events are grade 1/2 adverse events.

Pruritus and angioedema again were more common in the rituximab-treated subjects.

Secondary malignancies were observed in the Zevalin-treated individuals. 3 acute myelogenous

leukemias, 2 myelodysplastic syndromes were noted in the entire study set. One individual was also documented as having a meningioma. The onset of the secondary malignancies was 8 to 34 months following Zevalin therapy and approximately 4 to 13 years following the lymphoma diagnosis.

Prospectively the time points for the HAMA and the HACA's sampling were probably inadequate to assess the true incidence of the HAMA and HACA. The reason being is at the time that these trials were designed, I think the agency had not anticipated that HAMA and HACA formation could actually appear 6 months post therapy. We have reasons to believe that HAMA and HACA formation could be documented up to a year following initiation of such therapy. Suffice it to say that currently IDEC has incorporated longer time points in the ongoing studies, and because of these ongoing studies, I think that we will have to wait to really find out what the true incidence of HAMA and HACA response is for Zevalin-treated subjects.

But in the integrated safety analysis for which we have data on 211 subjects, there were 5 individuals who had positive HAMA titers at any given point during the therapeutic course. 2 of them had positive baseline HAMA titers. 3 of them developed titers post treatment. 3 subjects also had positive HACA titers at any given point

in the Zevalin treatment. 2 of these subjects had positive baseline HACA titers, and 1 individual developed HACA titers post therapy.

Looking at the adverse event profile from these individuals, they are not at all outstanding compared to the rest of the population.

70 of 349 individuals, representing 20 percent of the population, have died. 58 of them were due to progressive disease and 12 of them due to other causes. We have already talked about the two intracranial hemorrhages which we believe was related to the documented thrombocytopenia in these subjects. There were 5 myelodysplastic/AML subjects who have also subsequently died. 3 individuals died of pulmonary complications in the context of preexisting pulmonary disease such as COPD. 1 individual has died of coronary artery disease and had a cardiac arrest, and 1 individual had a pneumonia subsequent to salvage therapy following Zevalin therapy.

Overall Zevalin therapy can be characterized by a high incidence of cytopenias, and as mentioned, 55 percent of the individuals had grade 3/4 neutropenia and 57 percent of individuals had grade 3/4 thrombocytopenia. And the median duration of these neutropenias was approximately 3 to 4 weeks.

To review for you, the most serious adverse

events included the hemorrhages, including the 2 individuals who have died, the myeloid malignancies with the 5 individuals who have died. There was a percent of individuals who had grade 3/4 infections, and although most of the allergic reactions were grade 1/2, I think there is sufficient concern from the agency that we would categorize them as troubling adverse events.

Briefly I will now shift to dosimetry and biodistribution. The agency has received data on 179 subjects that were assessed for biodistribution imaging. There were five imaging time points obtained for these individuals. In summary, there was sufficient diagnostic quality imaging provided to assess the dosimetry for multiple organs, as well as imaging for known tumor sites.

The MIRDOSE 3.1 software was utilized to analyze these studies. Regions of interest for multiple organs with localization of radiolabeled antibodies, such as the heart, lung, liver, small intestines, spleen, and testes, as well kidney and bone marrow looking at the sacrum area, was performed.

Represented in this table is a subset of these analyses. First, the spleen, marrow, and liver, which I think are traditional organs commonly looked at in terms of maximum dose and potentially reflecting target injury to these organs. Represented here is the median dose for 32

millicuries to these organs. So, 1,350 for the spleen, 90 to the sacral region of interest for red marrow, and 547 centigrays for the liver.

The next three categories are categories that were of interest in the post-submission analysis performed by the FDA. During this review, it was uncovered that the testes were receiving a median dose of 950 centigray. As you've heard today, I think we would agree that it is possible that this number overestimates the measurements in the testes because of the limitation of the software. However, even considering the limitation of the software, we believe that substantive doses are likely within the testes, and although we cannot see the ovaries, they're possibly also involving the female gonads.

Represented here are median centigray dosages to the upper large bowel and lower large bowel. The reason that these are presented to you is because in almost all of the images that were reviewed at the FDA, we do see lymph node aggregates within the bowel imaging with the indium-labeled 2B8.

Correlated with the imaging of the GI tract is the numeric appearance that there's a greater number of GI toxicities within the Zevalin-treated therapy represented in the blue graph compared to the rituximab-treated individuals in the red bar graph. So, nausea, abdominal

pain, and vomiting were more common in the Zevalin-treated individuals. Please note that the majority of these GI toxicities were grade 1 and 2.

The FDA has also performed worst case scenarios using the existing data that was submitted in the BLA. In the modeling that we have performed, we have estimated that it is possible that adjacent normal tissue could have as high as 8,000 centigrays up to 1.1 millimeters into an adjacent structure so the potential dose that an adjacent tissue could receive could be as high as 8,000 centigrays up to 1.1 millimeters into that structure.

We have also modeled the data looking at alterations in the biodistribution and also obstruction of the clearance route for the Zevalin therapy looking primarily at potential outlet obstructions and delivering sufficiently high dosages to the kidneys where injury could be caused.

So, overall assessment pertaining to the dosimetry and biodistribution, I think we would agree that normal organ dosimetry supports the use of a fixed dose of yttrium-labeled Zevalin. In addition, the biodistribution we believe is necessary to assess normal organ and tumor site localization.

Another comment that I would like to make is that currently we feel that there is inadequate data to

assess the safety of additive localized radiation effects from external beam radiation therapy and Zevalin therapy. And I think Dr. Meredith alluded to that in her talk, that that additive effect could be serious and could result in significant morbidity.

So, briefly let me conclude that we believe that there is sufficient data to demonstrate durable antitumor activity, as was documented with overall response rate in both the efficacy studies, the 106-04 trial and the 106-06 trial. We believe that Zevalin therapy is associated with a significant hematologic toxicity in the majority of the subjects, and this can result in serious morbidity in the minority of subjects.

As compared to the Rituxan therapy, Zevalin was associated with a superior overall response rate. There was similar duration of response and time to disease progression. Zevalin also showed a 58 percent overall response rate in the rituximab-refractory individuals.

Data is, however, limited in the non-follicular subgroups and data in these subgroups is also limited for subjects who have not received prior Rituxan.

Thank you.

DR. NERENSTONE: Thank you very much.

I'm going go open it up now, questions from the committee to FDA. Yes, Dr. Taylor.

DR. TAYLOR: Could you clarify again? On the second malignancies, you saw five and they were all in the Zevalin, none in the control group?

DR. BISHOP: That is correct. The 5 individuals that I presented in my slide are from the integrated safety analysis in the Zevalin-treated subjects. I am not aware of rituximab-treated individuals.

Dr. White, do you have a comment to that effect?

DR. WHITE: There was a single patient on the rituximab control arm who developed a pancreatic cancer.

DR. BISHOP: That's correct, but none of the myeloid malignancies. I'm not aware. Again, that study arm was only with 70 individuals as compared to the entire integrated safety analysis of 358 individuals in the Zevalin.

DR. NERENSTONE: Just information for everyone who's wondering, to bring us back to the real world for just a moment. I'm getting things brought up to me, and as they come up to me, I will pass them on. One is that Camp David has been hit, and another is that there is a biological warfare threat. So, those are both confirmed I guess on CNN.

I know this is hard to keep to us concentrated, but since I know, I think it is fair for people to know.

And this afternoon's discussion will be canceled and postponed.

Dr. Levine.

DR. LEVINE: A question just going back to the myelodysplasia. What was the follow-up from the time of diagnosis or the number of treatments given in the Rituxan group versus the Zevalin group? I'm trying to figure out the myelodysplasia and is that due to Zevalin or is that due to all the other treatments and all the other times? So, how long was the follow-up and how many treatments given in the Zevalin group versus the Rituxan when you have, whatever it is, 5 versus 1, as far as the AML or myelodysplasia follow-up?

DR. NERENSTONE: Who wants to answer that?

DR. BISHOP: In the control study, the median number of therapies for both groups was, I do believe, two prior therapies in the Zevalin-treated and the rituximab. This number increases, I do believe, for the overall analysis, and I think it's three prior regimens for the overall integrated safety analysis.

I am not aware -- and maybe Dr. White would like to supplement this. Looking just at the 73 individuals in the Zevalin-treated arm and the 70 rituximab, I don't believe that any of these Zevalin-treated individuals were the individuals with the myeloid

malignancies. Is that correct, Dr. White?

DR. WHITE: If you restrict the analysis only to the phase III randomized trial, there was one pancreatic cancer on the rituximab arm and one myelodysplasia on the Zevalin arm. The median number of prior therapies on the various trials were either two or four prior therapies, with a range up to nine. And the median observation time for the safety population after Zevalin was about 2 years. That's median.

DR. NERENSTONE: Did that answer your question?

DR. LEVINE: No. It still doesn't answer it. In other words, I just want to know whether the Zevalin-treated patients have been followed longer than the Rituxan followed patients. That's my question. How long has each group been followed to see what's going to happen?

DR. WHITE: I understand now. The Zevalin-treated patients, if you count the entire group of patients that we submitted data on, 489, have been treated from 1993 to the present. However, the majority of those patients were treated more recently with a median follow-up of about 2 years.

The rituximab-treated patients that were in the 106-04 trial were only treated on that particular trial which began in 1998, and I would have to estimate that the median for that group of patients would be less, but we

would have to calculate it to know for sure.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: I have two sets of questions. The first does relate a little bit to the toxicity issues. A striking feature is the duration and the risk for morbidity that is of potential concern in the broad application of this type of therapy. So, I guess I would ask you, I guess primarily the FDA, in your analysis of the data provided with the dosimetry, was there any evidence that the people who had the more severe myelosuppression by one index or other had either a different feature to their dosimetry, a smaller tumor mass, any evidence of different behavior of the product?

That leads to the second set of questions. Are we clear that the robustness of the product elaboration and what is admittedly a somewhat more complicated procedure than we usually undergo is sufficiently reproducible that some wobble in that process might not be related to these toxicities?

DR. BISHOP: I will let Dr. Mills address the dosimetry issues.

DR. MILLS: From the standpoint, we saw no characterization amongst these subgroups that you're describing. The dosimetry unto itself, we were looking across in the representative organs, and we were not able

to discern that there was any difference in these response curves that you're talking about. Our concern frankly from that standpoint was to look at the normal organ dosimetry, and we did not break out any differences to them. We did not look across board. And I'll ask Dr. Bishop if he could comment in terms of the response characteristics you're talking about for the toxicity.

DR. SAUSVILLE: Specifically did the people who had more toxicity have less tumor volume, a lower mass?

DR. BISHOP: Again, I think it's important to note that the majority of the toxicities that we had seen were grades 1 and 2, with probably the most significant toxicity -- the grade 3/4 toxicities observed being infection in 8 percent of the study population. Clearly we believe that the incidence of infection was higher in the comparative arm for the Zevalin-treated individuals than for the rituximab-treated individuals.

Now, having said this, the other nonhematologic adverse events that we were seeing tended to be, when looking at grades 3 and 4, of low frequency.

Now, pertaining to your question, addressing whether or not tumor bulk may have been related to a pattern of toxicity, we are unaware that there was any predictable patterns that were observed in the data set that would relate tumor bulk with observed adverse events,

whether they were hematologic adverse events or nonhematologic adverse events.

DR. NERENSTONE: Dr. Blayney?

DR. KEEGAN: Could we answer, just for a moment, Dr. Sausville's other question?

I believe your question pertained to whether or not in the manufacture of the product, there were concerns about the robustness of the manufacture. And Dr. Shapiro can elaborate if you want, but she has said that to our satisfaction, the product can be reproducibly manufactured within their own specifications such that we did not observe great variability in the trial that would suggest that there was some looseness there or that makes us more concerned about the use of this in the community.

DR. MILLS: Maybe I want to express one extension from that. The difficulty that you're going to see in terms of this product is you've had a large multi-center experience, but you've not gotten it out in the community hospital. Part of the concern that you'll have, in terms of reflectiveness, is one of the elements within the biodistribution imaging that would represent for you another safety element, that indeed the ability to prepare the indium-labeled 2B8 product and actually observe the expected normal biodistribution is a safety element that indeed in the community hospital setting they'll be able to

verify. And if that fails, that's evidence they should not proceed. One of the concerns that you may have is that you'll be able to identify that on an individual basis.

DR. SAUSVILLE: So, again, I guess in the proposed labeling for this product, are there criteria that would tease that out? And do we have sufficient quality control out in the community that this type of thing --

DR. MILLS: In the presence of an altered biodistribution if a product fails in terms of breakdown, it's readily apparent to a nuclear medicine imaging physician where you see a significant loss of the blood pool evaluation. So, as a result, this is a fairly course and relatively straightforward element. You have basic standard production elements also, but there's another fail safe in terms of looking for that expected biodistribution and vascular component that would fail if indeed it was in a colloid form which would break down.

DR. SAUSVILLE: Again, just to pursue the point just briefly, where you're thinking leads, at least me, is that I have no doubt that a nuclear medicine physician in a research facility that's used to doing clinical trials with imaging of this sort would be very comfortable with the call that you're making. On the other hand, I think it would be incumbent upon somebody to make sure that that level of expertise is --

DR. MILLS: I think that information can be readily transmitted to any facility which would be using this type of product, even in the community setting. But from our standpoint, realize that you have such products as Oncoscint and Prostascint which are already out in the community. So, there is a fair understanding, in terms of the expected biodistribution of a radiolabeled antibody product on a diagnostic basis, and that's what you have with the indium.

DR. SAUSVILLE: I guess that's the key point. It's a diagnostic rather than therapeutic basis.

DR. MILLS: That's right.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: First of all, I'd like to say that your review was well organized and it was a pleasure to read. Thank you.

Second, you alluded to an adjacent organ toxicity of 8,000 rads or equivalent of 8,000 centigray. What organs did you simulate in your analysis?

DR. MILLS: In the analysis, we took several different models, pulmonary artery, simulated a small nerve such as the vagus nerve, also simulated the pericardium. Those would be elements where we would be concerned. The pericardium would be a structure which, indeed, if you put one of the example tumors, which we had one almost as high

as 25,000 centigray, adjacent to the pericardium in a theoretical model, we could put as much as 8,000 to 10,000 rads into that adjacent pericardial structure. So, there is a potential theoretical risk.

We did not see it in the clinical trials, but one should understand there is a potential risk to put that much radiation a millimeter away from the margin of the tumor. So, it's a concern for the morbidity to identify that it is a potential risk and especially in these early evaluations.

DR. BLAYNEY: The second question is, do you anticipate any inclusion in the label about patients who have received previous external beam or involved field radiation therapy as a warning or precaution to physicians who might be administering this product?

DR. MILLS: I would anticipate that certainly we're going to have to have advice because we know that we have limited data and that data is not adequate for us to really come down to fair conclusions from it. We've had a small, but good experience with this product to this point, but we need to have extensively more follow-up and more evaluations in the community setting as well to be able reflect what's going to happen in these patient populations. So, obviously a warning, an indication, information for the attending physician to realize that

this lack of data is there and to be aware of this concern.

DR. BLAYNEY: I don't know if it's appropriate to your simulations. Even though such a high dose hasn't been observed, I notice the dose range of adjacent organs is quite wide in the sponsor's material. Is it appropriate to warn physicians that may be treating large or even small mediastinal tumors adjacent to the pericardium, vagus nerve, and some of these other vital structures you've talked about?

DR. MILLS: It's quite apparent from doing these simulations, that the more this information we draw into the package insert, I think the better we're going to be. You're going to go from a small experience to a larger experience in the community, and for them to have adequate information and to realize what the theoretical model is is a very significant concern for us in terms of making sure we get adequate information out there. We don't have a lot of data yet in terms of it. As you've heard this morning, the dosimetry community is itself evolving as we speak in terms of these concerns and understanding how we're going to assess them.

DR. BLAYNEY: Maybe that community will read the package insert more vigorously than the oncologists.

(Laughter.)

DR. MILLS: I am certain they're going to have

full attention to it. At a recent meeting, they had quite a bit of attention already to it.

DR. BISHOP: If I may make one additional comment to that effect. I think having the indium 2B8 step incorporated into the overall therapeutic administration also provides the opportunity for a nuclear medicine physician, should he or she decide to do so, to perform some dosimetric analyses, especially if there was an adjacent area of particular concern. I think that having that in there, although we do not envision this being a requirement at this point, we also understand that there is that option should one decide to do so.

DR. NERENSTONE: I have a quick question or not so quick. It was a little disappointing to see that only one randomized trial is being submitted for full approval and that the basis of that one randomized study is really response rate. As we talked about, clinical benefit has really not been shown in a statistically validated way other than testimonials from the investigators, and we certainly see these patients and understand that.

The second trial that was submitted as a phase III, as you're quite aware, is really a phase II study in Rituxan-refractory patients.

I understand your attempt to get at patient improvement by your post hoc analysis that you suggested of

the duration of response with the patients acting as their own control. I'm a little bit concerned about that because that was an unblinded evaluation of duration of response. Would you discuss that a little bit as to how robust you think that indication is?

Certainly it makes us reassured that it's not worse than Rituxan. Do you really think we could say that it's better than Rituxan given all those concerns?

DR. BISHOP: Certainly some of the questions that we have before you today are seeking such advice from the committee. So, I'm not sure in terms of the clinical review team having really formulated an opinion on the latter portion of your question.

Let me try to address, in terms of the initial drug development program and some of the agreements that may have been reached over time with the agency.

We recognize the limitations of the studies that are before us, and we certainly share your concern about the number of subjects that have been studied in pivotal trials, especially when we understand that low-grade non-Hodgkin's lymphoma has a high prevalence when compared to other lymphomas.

The study population that we're looking at is, indeed, a relapsed or refractory patient population who have had multiple prior regimens, as high as nine prior

regimens. Although the median in the Zevalin-treated patients in the randomized trial was two prior regimens, I think the range was up to five.

These individuals tend to have fewer and fewer options as they continue to relapse with their illness. I think that we recognize that there's also a shorter and shorter overall response rate with sequential therapies.

This probably influenced the basis for our acceptance of at least looking at activity in terms of overall response rate. We were never satisfied that this would be sufficient by itself. I think it's important to try to extrapolate from the data some sense of clinical significance, and that I think is important for the committee to consider whether or not there is such evidence in some of the exploratory analyses that have been done in the two studies.

And we do agree that the second trial, which is labeled as a phase III, is really a supportive phase II study, and we understand the limitation of that trial as well.

DR. NERENSTONE: In this setting, just to ask on behalf of the committee, if the decision is that there is not enough information to support full approval, would accelerated approval with subsequent phase IV commitment be an option for this committee to recommend, or is it an up

and down on full approval?

DR. SIEGEL: The company has to request accelerated approval before we can grant it. Sometimes we ask if they're interested when we get such advice and they can come back and request it.

Accelerated approval would be approval based on a surrogate with a plan for confirmation.

Interestingly, in my experience with cancer drugs, it's not uncommon that an initial approval may be based significantly on response data in a treatment-refractory population and that the commitment for confirmation is a head-to-head trial perhaps in an earlier stage of disease.

Here we have a head-to-head trial in an earlier stage of disease. What you're correctly pointing out is lacking is a clear-cut clinical outcome as opposed to a response rate outcome finding. So, if the committee were to deem that was useful advice, it would be helpful for us also to hear discussion about what sorts of data the committee would find useful in confirming the clinical benefit and what sorts of trials the committee thinks would be appropriate to conduct in the future.

DR. NERENSTONE: Are there other questions from the committee to FDA? Dr. Lippman.

DR. LIPPMAN: To clarify Stacy's comment, again

in the early discussions between the FDA and the company, were the discussions of one trial versus two? Was that something that was worked out up front and deemed acceptable to do one randomized trial?

DR. KEEGAN: The discussions focused around a single randomized trial with good supportive data and durable overall response rates in the refractory population. That was the agreement with the agency. We did not require two randomized controlled trials.

In this disease, we didn't feel it was an appropriate standard to hold them to a survival endpoint in that it was a late stage of the disease in terms of where they were in treatment and the fact that there is no data that there is any therapy that actually confers a survival advantage. So, we felt that was too high a mark.

I will say that there was some thought that the time to progression data should have or would have confirmed -- there would have been an advantage confirmed on time to progression if there was, in fact, an overall response rate that was higher with a similar duration of response. And we were somewhat expecting to see that in this study as sort of internal consistency. What we found was that, in fact, in both arms the patients who had stable disease as their best response, that category of nonresponders, in fact, had a very prolonged of stable

disease. So, we really have not observed a time to progression advantage, which is something we were expecting in this trial and we thought would have been a strong confirmatory secondary endpoint.

DR. NERENSTONE: But we were also told that the study was not powered to look at that.

DR. KEEGAN: It was powered to look at substantial differences in time to progression but not to specifically exclude a smaller difference. Obviously, every study is powered, to some extent, to see differences if they're in fact very large, but we did not require them to identify a very specific difference but only to give us a qualitative evaluation.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: I think the other complication here, which is I think unusual, is that you're not really comparing two different therapies. In the Zevalin arm, you basically get one way of looking at it, almost half of the treatment that's in the other arm. So, again this leads us into somewhat interesting waters in terms of whether or not the usual rules for comparison or expectations for comparison are reasonable I think.

DR. SIEGEL: That concern is reflected, you might note, in some of the wording of the questions. We have a regulation regarding fixed combination therapies,

which arguably this falls into, and from a scientific point of view it has a lot of similarities, which would suggest that you need to demonstrate a contribution of each drug in the combination.

Here there's, I would venture to say, although I haven't independently researched it, very little if any data about what this dose of rituximab, this 250 twice, would do if done alone. I think the most we could say with comfort is that it's probably not any more effective than the approved higher dose of rituximab.

So, I think one of the things we're interested in determining is whether one can say from these data -- and I think this gets at the heart of what you were saying -- that this treatment offers benefits beyond that which would be seen by rituximab alone because from that, we can then deduce that the radiolabeled component is contributing to the therapeutic effect.

DR. SAUSVILLE: But by that way of thinking, it becomes in a sense a toxicity tradeoff. In other words, one of the features that's attractive about rituximab as a single agent is that it's very, very safe in terms of the usual things you worry about. On the other hand, while it is true that this could be considered less safe by some criteria, there is the evidence that was presented that there might be at least subsets of patients or individual

patients who obtain a prolonged response.

DR. SIEGEL: Right. From the point of view of that particular regulation, I would say what needs to be established is that it has a benefit beyond that of rituximab alone, not that that benefit is outweighed by the risk. So, we don't need, in order to able to approve it, to say it's a superior therapy overall to rituximab. We need to be able to say that there's a contribution.

I think then, though, we also, as with any approval, will look at the risk/benefit and say do the benefits of this therapy outweigh its risks. So, maybe I'm agreeing with you but wording it differently in light of our regulation.

DR. SAUSVILLE: But that's where in a sense the second trial, which is the comparison against, as it were, prior response to either chemo or rituximab -- although it's a different way of looking at things, it clinically addresses a very common scenario in the care of these patients because to have a meaningful response rate in a rituximab-refractory setting is noteworthy.

DR. SIEGEL: Right, we think so. In a lot of drug development, looking at refractory early in development, one of the approaches is in fact an open label study in treatment-refractory patients. Analysis of those studies is often, as in the analysis you've seen presented,

based on a presumption that simply repeating or adding yet a different related chemotherapy regimen would not yield a response better than the response to the prior cycle of chemotherapy, that based on a fairly broad, as I understand it, data set -- you all know better than I -- in a variety of diseases that recurring rounds of chemotherapy tend to give diminishing returns. So, if you see something that surpasses the preceding cycle, you can presume that that's better than you would have received by simply another drug or repeating the prior drug.

Now, there is certainly less data about repeating rituximab in this setting, but one might -- and this is sort of at the heart of the question -- be willing to presume from that study that a repeated round of rituximab would not give a better response than the prior round of rituximab did. If that presumption is correct, there are regression to the mean issues. There are a lot of issues here that you could question. But if that presumption is correct, then this comparison showing a significant response rate, as well as the one showing more durable responses, suggests a significant activity.

DR. SAUSVILLE: Right. But to be clear, there would be very little clinical enthusiasm, given the definition of Rituxan-refractory that was used here, in retreating patients with Rituxan.

DR. SIEGEL: And that's why it's hard to do a controlled study in that setting. You almost have to do this design because nobody wants to randomize to a treatment that hasn't worked in the past.

DR. NERENSTONE: Are there any questions from the committee to FDA?

(No response.)

+ DR. NERENSTONE: If not, then what I'd like to do is open the discussion of the committee. I don't know if Dr. Bridges, Dr. Sausville, or Dr. Levine would like to start out. They're our invited consultants. Comments? Dr. Levine?

DR. LEVINE: I'm not worried about what was last stated because the data was very careful in the real nonresponders to Rituxan. That was a 51 percent response rate on the Zevalin. So, I'm very comfortable thinking that the Zevalin will work when Rituxan doesn't.

One of my concerns relates to the broader indications, including the transformed cell. I have real difficulties on that one for several reasons.

Number one, it's a total of 9 patients, which you can't say anything. An example of the fact that if the numbers are too small, it doesn't mean anything, is the concept that they've got a 75 percent response rate to Rituxan alone in transformed cell lymphoma, and if that's

valid, then I've been treating my patients wrong all these years. So, I think the numbers are just way too small.

In addition to the fact that the numbers are too small, their data show that in fact Rituxan was superior to the Zevalin, if you want to believe those small numbers. So, I think we need a lot more information on the transformed cell group.

On the IWF A group, I could make the same comment. The numbers are about the same, i.e., very, very small. Personally I don't have the same problem with that group, however. They have shown in those very small numbers that in fact the IWF A group treated with Zevalin did do better, did have a higher response rate than the same group treated with Rituxan alone. That's more reassuring to me. In a biologic sense, I'm comfortable as well that it's the same biology, as far as the disease. It would make sense to me that it might respond. So, I don't feel as strongly on the IWF A group as I do on the transformed group.

Moving around a little bit, I am concerned about the AML/MDS, not to the extent of believing that this product should not to go forward, but certainly with the belief that this must be very carefully looked at over the years to come.

That kind of colors my view as it relates to

the pediatric indication as well. I'm worried about it. I don't think there's a major problem here because follicular lymphoma is so unusual in children. So, I don't think it would be a big hit to say, no, let's just leave the children out of this for a moment until we see the long-term effect of the radionuclide conjugated product, especially considering that the product would be used in people who had failed other regimens.

So, I'm uncomfortable about the indication for children. I'm clearly uncomfortable about the transformed. I could be swayed in either area I guess on the IWF A, and then wanting follow-up data on the MDS/AML.

There may be other comments and maybe I could come back and say those later when I think of them.

DR. NERENSTONE: Thank you.

Dr. Bridges.

DR. BRIDGES: The one issue of external beam toxicity with this treatment would be a concern to me that even though limited and there's no clinical evidence about these high doses to adjacent structures, that somehow that would have to be communicated to the radiation oncology community. There would have to be, I think, a vehicle there.

I think if there were possibly some modeling -- an additional -- in maybe several paraspinal tumors in the

periaortic region adjacent to the spleen with your modeling capability to educate the radiation oncology community on the potential dose there.

Those would be the two factors that I would think could be looked at.

I don't know. There was no comment about spinal cord. It was omitted as a normal tissue, an organ that was looked at, as far as the dose to the spinal cord in this study. And I don't know if it was a limitation of the computer model or picking a site in the spinal cord to dose, but I think that would be something that needs to be put out to the radiation oncology community.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: I agree with the comments of my esteemed colleagues and I particularly agree with the characterization of the relatively small database to generate enthusiasm for the nonfollicular lymphoma subtypes.

I guess I also, on the other hand, think that there are certain elements to the optimal use of this product that can only emerge from further clinical trials.

It remains unclear to me, and I guess it really wasn't looked at in any of the material that we were presented. CD20 is assumed to be the same in its expression level in all comers. I think that's uncertain

even within the world of follicular lymphoma. I think it will be interesting as experience emerges, if there are additional studies, of whether that can be honed in on with some greater precision.

I've already commented on the concerns that I have that if this is used in a general sense, that very clear ability to define the capacity of the receiving, more community-oriented oncology setting be supported in their optimal application of the product.

Beyond that, though, I think the sponsor is to be congratulated for tackling a difficult problem and clearly reaching some very interim fascinating and potentially valuable outcomes for some patients.

DR. NERENSTONE: I have a question that probably is going to have to go back to the FDA. We're not allowed to consider cost in our evaluation, but certainly if you look at difficulty in giving this medication, especially in the community, it's really not one dose. It's really Rituxan, then at least two follow-up imaging studies, then Rituxan and the therapy.

According to the sponsor, they had no problems after the imaging to change their decision to give the dose.

Is there going to be central monitoring of these initial images to know at what point they are no

longer needed, or is this just going to be in perpetuity that we have to do these indium studies? I think the complexity it adds and the cost it adds really can be considerable.

DR. BISHOP: I'll lead off probably with a comment relating to one of your questions which pertains to what additional studies can be performed in terms of making us comfortable that the imaging portion of the Zevalin therapy is no longer necessary. I think that's one of the questions to the committee today. So, we're certainly looking for input from you in that regard.

It is not entirely accurate to say that there's no experience in which imaging studies did influence clinical decisions in the overall study experience. We are aware of at least three instances in which clinicians did make decisions, based on the images that they were seeing, not to continue with the yttrium administration. None of those instances turned out to be because of unsafe dosimetric evaluations when these images were subsequently reviewed in a centralized area. But there were some concerns with at least 2 of the patients that they may be unsafe dosages to certain organs. Again, this was very early in the overall experience with Zevalin.

And there was a third case in which there was at least a distribution of the indium-labeled antibody that

was not concordant with the known distribution of lymphoma in which the physician subsequently decided not to go ahead with the therapeutic administration of Zevalin.

DR. NERENSTONE: Would the sponsor like to add anything?

DR. WHITE: Yes. Just a point of clarification on two items.

The first item, with regard to Dr. Bishop's description of the three cases where imaging was used or dosimetry was used in a decision to move forward or not to move forward, the first of those cases was in the 1993 106-01 trial where the dosimetry specifications were different, and it required that the ratio between the dose to the tumor and the dose to the highest organ was of a certain magnitude. In that patient, because of a liver dose of 900 relative to the tumor dose -- this was an intermediate grade patient -- the dose was not given. So, it's a little different situation.

In one patient, the imaging was looked at with regard to a SPECT scan because of underlying retroperitoneal imaging, and the decision was made to go ahead and treat.

And in the third patient, there was a decision by the investigator, because of a single functioning kidney, not to go ahead and treat, although it met

dosimetry requirements.

Another point of clarification with regard to the CD20 distribution. If you would like, Dr. Horning is prepared to address this as well. But to our knowledge, there is greater than 95 percent, virtually all of the patients with low-grade nonfollicular lymphoma, do express CD20 and also the majority of patients with transformed lymphoma, although the intensity of expression in the low-grade nonfolliculars can be lower, particularly in those who have small lymphocytic lymphoma.

DR. SAUSVILLE: Right. So, you raised an interesting issue though. I actually agree with those numbers, but if you were one of the 5 percent, is that a problem? Number one.

And number two, there's the intensity issue. Being positive might mean 5,000 per cell or 500,000 per cell. The dose that's going to be given to the tumor is different.

DR. WHITE: Acknowledged.

One last point of clarification. In the rituximab-refractory trial, the comparison to the prior therapy was prospectively defined in the protocol prior to opening of the protocol. The additional different methodology was defined by FDA later on. But there was a prospectively defined comparison that was also performed

and also had the same exact results.

DR. NERENSTONE: You're talking about the duration of response question?

DR. WHITE: Comparison of the overall response rate and duration of response to prior rituximab in prior therapy.

DR. NERENSTONE: Dr. Keegan.

DR. KEEGAN: Dr. Nerenstone, to get back, we believe that it's possible that there may be a body of evidence that might be convincing in terms of telling us when one might omit that initial imaging step. Our concern is that the database is so very small that we don't have a very good estimate of how often, in fact, alterations in biodistribution might occur, although it certainly must be in a relatively small number in a carefully selected population, as we've seen in the study. Whether that represents the patient population at large that may be exposed to this drug is again another issue that we have.

So, what we're seeking from the committee is what are the types of patient populations we should focus on and what level of alteration of biodistribution might be considered acceptable for this type of therapy so that we could decide what the total numbers of patients and the types of patients are that should be studied to gather this data and reassess.

For example, at this moment, we couldn't say that we could exclude an incidence of 1 percent altered biodistribution even in the population that's screened in this studies. Is 1 percent of altered biodistribution acceptable? Or missing that, would that be acceptable or would that possibly not be acceptable.

So, we would need some discussion of what we should be focusing on. And we raised some of these issues like prior exposure to murine proteins and prior exposure to chimeric proteins possibly as well, Rituxan in particular, as well as whether there's some incidence of altered biodistribution which you would find unacceptable, so unacceptable that we should not consider removing the imaging.

DR. NERENSTONE: But there's nothing so far to think that you might.

DR. KEEGAN: I think the experience is too small at this point, but the question would be, at some point, would there be a robust enough experience that would give us a level of comfort that the incidence could be lower than 1 percent, say, and would that be sufficient in your minds to consider removal of the imaging step as a screening procedure.

DR. SAUSVILLE: I think this gets back to the point that's come up in different ways throughout the

morning, that although the imaging was used and was certainly reassuring that everybody imaged the tumor, and there was acceptable biodistribution, we nonetheless really didn't see hard and fast criteria that were applied prospectively. I think that's something that I presume the agency would work out with the sponsor if this goes forward in a way that addresses some of the concerns related to distribution and one might even say lighting up of a mass in the first place. In the unexpected event there was reasonable distribution, but the mass didn't reach a ceratin level of brightness, as it were, one could imagine that as a criteria not to go forward as well.

DR. MILLS: I think also the committee should consider the concern that we've heard this morning. It's the potential that we may develop subsets in terms of the tumor distribution and where it's imaging and other potential organs at risk adjacent to it. You may see in the next several years criteria that would align for further evaluation with biodistribution imaging, maybe even dosimetry for tumor distribution within the mediastinum adjacent to the pericardium or in the retroperitoneal area or adjacent to the paraspinal region as these models are evolved. We've had a limited amount of data on a limited number of patients, and much of this information will evolve.

That's why at this present time, working through the biodistribution imaging and working through the medical community, as well as through the sponsor to gather further data, I think is going to be in everyone's interest to be able to gather that information and then come back with a more informed opinion in terms of where these elements may or may not be necessary in patient subgroups.

DR. NERENSTONE: So, this is not an issue unique to this one product. This is going to be an ongoing issue as we evaluate more of these monoclonals.

DR. MILLS: Yes.

DR. NERENSTONE: Okay.

DR. SIEGEL: I would just add to the discussion, since your question mentioned and the complexity mentioned the use of the cold rituximab, that as our discussion has talked about and our question addresses what data might be necessary to allow us with comfort to think about not using the initial imaging or biodistribution step, that that is a different question from what might allow us not to use that initial rituximab dose which may be contributing to the therapeutic effect, may be lowering immunogenicity by depleting B-cells, may change biodistribution of the radiation by changing B-cells, we would need, I think, data about a single day type therapy before we would consider that --

DR. SAUSVILLE: As was pointed out by one of my colleagues to my right, it's possible that there's an element of interference actually with --

DR. SIEGEL: Yes.

DR. SAUSVILLE: And that's a matter of future trials.

DR. SIEGEL: That synergizes.

DR. NERENSTONE: Dr. Lippman.

DR. LIPPMAN: I'd just like to ask Dr. Sausville to clarify for me. You seem to have a lot of concerns with the available data. Clearly it's extremely provocative. It's an active drug. That's not the issue, but you seem to be framing things that you're very concerned with the application of this agent as it's being evaluated now, not the idea that future studies would ask different questions. Normally when that comes up or often, that's the basis of accelerated approval. We think that it is going to lead to clinical benefit, but there are a number of concerns remaining, particularly in the context of one randomized trial.

So, I guess I was wondering how concerned you are with this. Again, this also gets at the issue that Dr. Nerenstone raised about how important are these subsequent studies to the safety of these patients.

DR. SIEGEL: Before we move on with that, let

me just provide a little bit of clarification about the accelerated approval regulation. Accelerated approval does not change the standard of evidence or the standard of proof that, in effect, is present. That remains the same, substantial evidence from adequate and well-controlled trials, as it is for a regular approval. It just allows that standard to be applied to evidence based on other than the ultimate clinical outcome and in some cases surrogate endpoints other than clinical endpoints altogether.

So, just so we're clear, because there are potentially two ways of looking at this, accelerated approval may be applicable if we're convinced about an effect on response rate and not about an effect on clinical, but it's not to be used because, well, we're almost convinced about an effect but we're not quite sure about that effect per se. So, it doesn't lower the standard. I'm not suggesting your comments implied otherwise. I just want to make sure that we're all on the same page.

DR. LIPPMAN: No, I didn't imply otherwise. This is clearly an active drug. There's no debate even from someone who doesn't treat these kinds of patients. But it was very clear.

But I am concerned about the clinical benefit issue because of the concerns that Dr. Sausville raised.

In an accelerated approval, there are mandated phase IV studies to look at some of these things, continue trials. That's what I'm trying to get the level of that issue from one of the experts.

DR. SAUSVILLE: Well, to comment, I think that part of the questions that I've explored in the course of the morning was this issue of the nature of the product because it is breaking new ground in what potentially would become widely available, namely, a targeted radioisotope for treatment as opposed to diagnosis. And our FDA colleagues have looked at this pretty thoroughly at this as a product. So, if they're convinced, based on the evidence at hand, that at least in the centers in which it has been used in a more research oriented sense, that it performed well, I take that as very encouraging and would actually encourage its more wide dissemination.

But I think what I tried to emphasize is that because these concerns in product utilization exist, is the isotope bound to the antibody, when we get more experience with biodistribution in outlying sites, whether the biodistribution curves and the agreed to label comparable populations of masses are actually looked at, that that be folded into a consideration of how best to use it and to really, as I said before, support the broader community in using it. That's my concern. It's not that there's a

concern about the nature of things. It's how it's going to be ultimately translated.

With respect to the issue of benefit, in the rituximab-refractory population it's very provocative and impressive data even though it represents the level of response. I share Dr. Levine's concerns that in the other histologies we don't have as firm a notion of what potential value it might have simply because of the numbers. That's something that, again, might be part of future trial endeavors that could lead to an expansion of the indication on more solid evidentiary grounds.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: A few comments. First, I want to commend the company on having an open access program folded right in and keeping it open during the regulatory review period. It should be a model for the rest of the pharmaceutical industry.

I am somewhat concerned about the toxicities, the hematologic toxicities specifically. But in fact if you look at the response rate of combination chemotherapy, the only ones that would give you something similar to this is going to be ICE or CVP which has similar hematologic toxicity and a lot more nonhematologic toxicity. So, I think if a doc knows how to deal with prolonged neutropenia, it will be fine, but if they don't, somebody

has to teach them before they're going to be able to use this drug.

Having said that, I noticed in your backgrounder that a lower dose actually gives the same response rate in your phase I/II trial, and at some point someone should consider whether or not a lower dose should be explored with less hematologic toxicity as well.

I am concerned about whether or not the bone marrow should be harvested before this drug is given as we do with any other kind of radiation. I was not happy to hear any detailed information about CD34's or the number of apheresis to collect blood stem cells in patients who were treated. That would have made me more comfortable about making any comments about getting harvests done before this drug.

I was surprised to see that there were no complete responses in patients who were truly Rituxan-refractory since the indication being sought was for Rituxan-refractory patients, that all the CRs were in patients who were relapsed after a short period of time after receiving Rituxan.

On the other hand, the response rates in the follicular lymphoma patients are spectacular, and I have no doubt that it's the radiation and not the antibody that's doing this. That's pretty clear.

I think I am convinced that there will be a clinical benefit seen, if more patients were put on the study, since the curves for time off chemotherapy and time to progression, which are two hard and fast measures of clinical benefit, are pretty wide, and if the numbers were greater, the p values would probably reach significance.

DR. NERENSTONE: Dr. Levine.

DR. LEVINE: I just wanted to comment as well on the concept of clinical benefit versus response rate. From basically a history of caring for these patients, I accept it's not one dose one time. On the other hand, it's about a week, and given the fact that there's a week of treatment and the rest is yours, it would seem to me that this is a major clinical benefit, and I personally would be translating the response rate into a clinical benefit.

The objective data that they do have is small -- i.e., not all the patients answered the quality of life instrument and so forth -- and yet that correlates with the gut sense of what we're all hearing, what the people have written and said to us. So, frankly, I'm not at all worried about the concept of clinical benefit. I think it's there. They aren't being treated and the tumor responded very nicely.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Thank you.

Again, I think this is a good drug and the sponsor I think designed some clever trials to prove it.

I'm concerned. I think the myelodysplasia is going to be more of a problem than we've seen today. The 2-year follow-up is relatively short in the lifetime of lymphoma patients who in this country now have received a lot of alkylators. So, it is what it is, but I think we need to all be aware of that.

The clinical benefit has not been established by formal means. I think we've heard today both surrogates for it in terms of time off chemotherapy and also testimonials from very experienced investigators using it. But I'd remind the committee, and also in our duty of just trying to fulfill our regulatory requirements, that we haven't seen a clinical benefit demonstrated in the hard and fast rules. Nonetheless, I think I agree with both Dr. Levine and the other investigators that there is likely to be clinical benefit conferred by this agent.

DR. NERENSTONE: Any other comments? Dr. George.

DR. GEORGE: I would like to complain a little more about the sample size, I guess, because both the sponsor and the FDA were in on this from the very early days.

Some of this could have been anticipated. The

design was to pick up a 25 percent difference in the overall response rate, which is remarkably similar to what was observed. So, it's fine. It reveals a strong statistically significant difference.

However, if you take a negative view and look at what kind of response rate might you have excluded for sure, the lower confidence bound is about 9 or 10 percent. If that had been observed, it might have, of course, colored what you're thinking, if that is the truth, not what is observed.

The same way with the time to progression. It was looking at clinical similarity, which means I think the eyeball test. You know, it looks close to me or maybe even a little better. But again, if you look at what you've excluded, there's still a reasonable possibility that in fact it's worse, even though it looks better now, in terms of time to progression even.

The third point about the sample size issue or the size of the studies is the issue of the histology. About 80 percent were follicular and the rest were roughly equally split into low-grade and transformed in the first study. This I think could have been anticipated or at least been guarded against some. If you do a trial and you really think you're going to be concerned about the results in all of the subgroups, as opposed to simply stratifying

for the purpose of getting the balance and doing a little more efficient test -- that's one of the questions before us today. Is there any effect here in some of these very small subgroups?

This could have been anticipated some. You get these small numbers. It doesn't matter what they are. You're not going to find a difference. I'd just point out in the transformed group, I think there were 9 on the Zevalin and 4 in the other group, and 3 of those 4 responded. That's fine. But what if it had been 2 of 4? Well, then suddenly it's worse.

This could have been anticipated, and when you're at the end of the trial and you did it in a stratified way and you didn't anticipate it ahead of time, it seems to me you either buy the whole package or you don't with respect to the response rate.

One minor point about this I just noticed -- it's a question I should have asked earlier I guess. This first trial was stratified, but was the randomization also blocked in terms of numbers in each group? I guess it was.

DR. LANDIN: I'm Rick Landin, the biostatistician, and yes, we did block it.

DR. GEORGE: What was the block size?

DR. LANDIN: 8.

DR. GEORGE: Too bad it was 9 and 4. If you're

going to have a small group, it would have been better to have it a little smaller.

These are just random gripes about putting us kind of on the spot here now with these uncertainties.

DR. KEEGAN: With regard to the sample size, we did agree that if they demonstrated a 50 percent increase in the response rate or the delta of 25 percent, which they did, that that would seem to be fairly robust evidence of superior activity. At the time they designed the trial, we all recognized that they did not have clear ideas of what their targets were going to be in the study, as I recall, had a built-in interim analysis for re-estimation of effects in sample size, so that the study would have actually likely have been altered if they were seriously off on this.

When the interim analysis was performed and it suggested that they were adequately powered for the delta they were seeking, which, as I said, was about a 50 percent increase in response rate over Rituxan, the sample size as selected remained.

You're right that if we had concerns about the transformed data set, again it was essentially a risk that we allowed the sponsor to take by saying if the transformed patients behaved similarly and you have a large number of them, then the trial will be successful, and if not, then

the trial will be unsuccessful and that is your risk to take.

In fact, what happened is we simply feel that we don't have a lot of information, and there was some level of discomfort with how well one should extrapolate to that data set.

With regard to the confidence intervals, we had some lack of clarity. The confidence intervals around the response rates, in fact, don't overlap. The difference is small. We've not powered studies based on --

DR. GEORGE: That's true. I'm just pointing out the confidence interval on the difference is a lot smaller then the observed difference, obviously. It's a wide confidence interval.

DR. KEEGAN: It's a wide confidence interval with the small numbers. Correct.

I guess we would like again to get back to the time to progression. Again, this may reflect some of our lack of understanding about the effects of Rituxan and how prolonged they were since that in itself is an active agent. We didn't have a wealth of data at the time. But, in fact, when we didn't require that the time to progression data -- that the study be powered to also show a difference in time to progression, in fact, as you look at the curves, the data do show a fairly healthy trend in

terms of the difference, particularly again in that follicular subset.

I believe the company may also have the data on the combined nonfollicular and follicular subset as well, excluding the transformed. I don't know if it's quite as strong, but the trend did seem to be there and to be supportive. So, we considered that in addition as we looked at this application.

DR. NERENSTONE: Dr. Lippman.

DR. LIPPMAN: The comment that Dr. George made made we think again about other kinds of situations we've had on this committee. When a study is done like this, it is usually an all or none. You design the trial. It's randomized. And did it work in that population or not overall? Since this is going to come up in the labeling recommendation, I'd like to discuss this, although Dr. Levine made a very compelling case, if really the biology is there.

But in a sense in a small subgroup -- because we're not talking about a question of ER status in half of the patients -- a small subgroup of patients, to remove that group and say that this is not recommended would be a little inconsistent with some of the other aspects. The way this trial was designed, there are some differences. They're small numbers, but there was activity in both

groups. So, I'd like to get Dr. George's thought on that because it seems to be a major issue in what we'll discuss in the labeling.

DR. GEORGE: My response is clear from the statistical point of view: you include them or you don't. You prove this as stated or you don't unless there is something that has come up that is so compelling from a biological viewpoint that should have been thought about ahead of time, that you shouldn't have had these patients in on this study because they're just completely different and you couldn't have expected them to do the same.

In this case you did. You kind of threw them in there. Maybe you thought that overall they would be a little different in the overall effect but you stratified because you just wanted to have balance and do a little more efficient statistical test. But the result is an overall result. That is, it works or it doesn't work in this group of patients.

DR. LIPPMAN: So, my question is, what has come up since the design of this trial that was approved by the FDA and now that would lead us to select out that small population where we saw substantial responses in both groups?

DR. SIEGEL: I would say, first of all, that the FDA has -- and I'd ask my colleagues who were more

involved in the design of this trial, which I wasn't -- consistently identified that subset as a distinct subset that needs distinct data in its own right. As Dr. Keegan said, there was a risk taken as to whether those data would be adequate.

I think there are biological and regulatory reasons that are compelling to look at, at least the transformed subset, differently. One is that this therapy targets CD20, and those patients do not uniformly express CD20, and as a result they had a different admission criteria. I'm not sure if this came out or not, but those patients all required prescreening to be shown to be CD20 expressors as an entry criteria. That wasn't the case in other patients.

And these are not new factors since the trial was designed, but it's certainly a critical issue regarding interpretation of this trial. Part of this therapy is rituximab therapy, and rituximab is approved for follicular but is not approved for a transformed set. The sponsor, as I recollect, didn't seek that approval and didn't provide data in that group. I think this committee felt and the agency felt at that time that also was a separate indication requiring independent data, not so separate that data on other types of NHL are irrelevant by any means, but separate enough that one needs to look specifically at that

population.

So, I would argue that this is by no means a post hoc subset, nor was this trial designed without, I think, all parties realizing that there was a real possibility of significant response differences in that subset.

DR. LIPPMAN: Since I guess it's not based on new biology, it puts the committee in a little awkward position because it would be nice if this was clarified up front in the protocol and this group was going to be looked at differently. To just put them into a study that is not a huge study -- it's an excellent study, outstanding, and moderate size. But there are a lot of these patients. If that was a concern, it would have nice if that would have been taken into the prespecified analysis plan.

DR. SIEGEL: They were stratified separately, were they not? I'm sure the analysis plan speaks of a separate analysis. I haven't seen it, but I'd be shocked if it didn't, if that's what you're implying. They were stratified separately.

DR. WHITE: The reason that CD20 positive was required for the transformed subset was because at the time of the design of the trial, there was a single patient who had received Rituxan and at transformation became CD20 negative. This was published by Stanford University. At

the time, people didn't know how often the transformed patients could potentially be CD20 negative at transformation.

Subsequent to that, Dr. Maloney who was at Stanford at the time -- and I don't know if Dr. Horning is still with us here to address it -- it's been looked at. In fact, these patients are virtually always CD20 positive.

Now, it was stratified at the time. We had information in intermediate grade diffuse large cells. There were one or 2 patients in that group that were transformed, but the information that we were going on with regard to the activity in transformed disease was based on similar antibodies, but not the identical antibodies. So, we stratified so that we wouldn't be in a position where we had all the patients that were transformed on one arm and not on the other just in case there was any difference and then you wouldn't be able to tell whether it was because of that or not.

One last comment and that is, as you've seen from our briefing document, we also in a prospective way looked at every single prognostic factor that has ever been published in the literature with regard to lymphoma, breaking down the bulky disease, breaking down the bone marrow involvement, breaking down the extranodal disease sites, breaking down the demographics, breaking down

splenomegaly, et cetera. In some of those groups that are really small, we didn't show a statistically significant difference.

But our understanding was, as spoken by the statistician on the committee, that one understands that when you start to do subset analyses like that, that you may find a small subset where you're not demonstrating a statistically significant difference, but that the presumption is this isn't the entire population you're studying. They have in common that they have low-grade follicular or low-grade follicular, transformed at least in part of the body to a higher grade, and that especially to an immunotherapy or a biologic therapy, one would hope that the range of responsiveness that you would see would be similar among those types of histologies. Obviously, some patients have poorer prognostic factors than others and that can sometimes influence response. So, that was the thinking at the time of design of the study.

DR. NERENSTONE: Dr. Lippman, a follow-up?

DR. LIPPMAN: Can I rephrase the question a little bit? What would you have wanted us to see in this small subgroup of patients that would have made it more convincing to you that we wouldn't separate these out? In other words, we knew it would be a small subgroup. They were allowed to be included in the study, which should be

evaluated on the whole. There were major responses in both groups. It wasn't significantly different. So, can you give me a scenario where we wouldn't be having this discussion and we'd all agree that it should be used? 100 percent response in both groups?

DR. SIEGEL: I'm not sure there's any scenario or we wouldn't have this discussion. You have a different scenario, for example, in the IWG A and the transformed. I think it's worthwhile having the discussion. I think whether you consider transformed part of the same indication and you don't require data in transformed to give that indication or whether you consider it a separate indication is, I think, an issue that ought to be discussed regardless of what the data show. The fact that the data did not show a trend toward a higher rate in this subpopulation or to other better outcomes I think adds information to that discussion.

But I'm not exactly sure what you're asking. I think we're asking you for advice.

(Laughter.)

DR. LIPPMAN: I guess what I'm trying to clarify is that normally in every study that we review here, we look at the group as a whole unless there's some biologic change or whatever. We don't dissect out these small subgroups. I guess what I'm saying is nothing has

changed in the biology. It was allowed to be included and the differences were not significant and there was activity. So, that's what I was getting at.

DR. SIEGEL: Maybe I can ask the company. I assume that there was a prespecified analysis or analysis by histological type. Right? This was a question of concern, getting a confirmation. So, it existed and the design rolled in, but it also existed in their prespecified hypotheses that we wanted to check to see where we stood in that regard.

DR. LIPPMAN: And they weren't significantly different.

DR. SIEGEL: Well, there's not a statistical significance between 3 of 4 and 5 of 9? Is that what you're asking?

DR. LIPPMAN: Right. That's the obvious point with the small numbers.

DR. WHITE: It was prospectively designed as a secondary endpoint that we would analyze by histology, by gender, by age, by bone marrow involvement. We had a list of variables that we had used in our prior rituximab studies and were all of the ones we find in the literature, LDH, et cetera. So, like with those variables, we did do a prognostic variable analysis and looked again with the Breslow-Day and the Cochran-Mantel-Haenszel tests.

DR. NERENSTONE: Dr. George.

DR. GEORGE: Yes, I just wanted to add one more thing on this point. My point was for the committee for our regulatory considerations, if we do anything differently with this group, we have to be very clear it's going to be based on some kind of a priori biologic notions that this is completely different not from the data. This data is totally inconclusive on this point, and we knew it would be from the beginning.

DR. SIEGEL: I would add that there is the design of this trial, but there are also trials that precede and follow it. So, if your assumption is that there isn't a biological difference and notwithstanding the fact that rituximab hasn't been studied in transformed, then I guess we would revisit the decisions regarding that population for that and for future trials as well. So, you can advise us what's appropriate with the study design.

But I think also bear in mind that we're talking about development in this field, and I would like to be clear. If that's the advice of the committee that this shouldn't be considered a separate population, that we need separate data and we should just presume the same, then that's advice that will be valuable advice and impact other regulatory decisions as well.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: Yes, I would just comment in relation to this discussion. Unfortunately, we don't have ways of recognizing subtypes of breast cancer, lung cancer, et cetera that have accepted differences, as it were, in biologic behavior, at least as accepted differences. I think in the case of lymphoma, we do have. Even though they're all CD20 positive and therefore were certainly appropriate from a scientific point of view to be in the study, from a clinical point of view, there are nuances in the behaviors that now we are faced with asking is the number of patients, as I interpret your question, that have these sufficiently large that we can feel confident about conclusions related to the subset. I think the discussion that went on previously emphasized that we probably can't really feel confident about, for example, the transformed, and I think that's more or less a reality of the types of lymphoma presentations that we have.

I think the questions do actually provide an opportunity to comment on whether or not that should be considered in making the final labeling indications.

DR. LIPPMAN: But I think my point is that normally to exclude a small subset, you have to feel very confident that they're different, not that confident that they're the same.

DR. SAUSVILLE: I feel very confident that

transformed lymphoma patients behave very differently.

DR. LIPPMAN: To this treatment.

DR. SAUSVILLE: Biologically different. In terms of this treatment, we don't know.

DR. LIPPMAN: Well, but that's the point because they were included in the trial. You normally have to feel very confident that they're going to respond differently to remove them and not analyze them the way the trial was designed.

DR. SAUSVILLE: I mean, I feel confident that we don't have enough of them to know. That's the only thing that I know.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: I too am troubled by the small numbers, but I think several things we ought to keep in mind. One is that they were included, we're told, because they had the CD20 histology on the cell surface. So, there was some screening and there's some reason to think they biologically are similar to the other much larger groups.

Secondly, this is a therapy that's designed for near misses. Often the transformed lymphoma have the low-grade in close association with an intermediate grade or what we think of as this transformed histology. But this therapy has a tissue penetration of 5 millimeters, we're told. So, there is some near miss use of this as a

therapeutic agent for closely approximated cells that may not express the CD20 marker.

DR. NERENSTONE: Dr. Levine.

DR. LEVINE: I guess I just want to repeat again that I am uncomfortable really on the transformed group. They may have CD20 positivity, but it's a mixed bag biologically. Some of those patients have additional chromosomal aberrations or molecular aberrations. Some of them, in fact, are de novo transformed. It's a very mixed bag.

My concern is not just that we have very little data, which is true. The data we do have on one of the slides is on page 32. Of a total of 15 patients, the overall response rate, 40 percent. I can't say that that's different, but it's not 90 percent.

The other piece of information that I didn't have that would be important to me is if the patient with transformed lymphoma is treated and doesn't respond, then what we would do clinically is multi-agent chemo. That's exactly where you're going to use the multi-agent regimens and so forth, and that's exactly where you're going to do bone marrow transplant. I had asked the question, how many of the transformed patients then went on to chemo and how did they respond to chemo or what were their harvests like, because that becomes very important information clinically.

So, it's what you would do beyond the Zevalin in those patients who don't respond to it.

DR. NERENSTONE: But I'm not sure what the sponsor has to say really matters because it's very small patient numbers, which is getting back to your point.

DR. WHITE: We did analyze that data since you asked that question. We brought our database with us and I can answer that question now.

Let me just say since 5 percent are transformed at 5 years but 90 percent by the time of death, patients transform more over time. So, by definition, they have more chemotherapy over time. In a way, it's sort of a surrogate for additional chemotherapy. Maybe that may be related to the chromosomal abnormalities and the poor prognosis.

We did have 5 patients in the transformed group that went on to additional chemotherapy. 1 went on to DHAP. 1 went on to CHOP. 1 went on to ESHAP, 1 methotrexate. 1 was just Decadron. So, actually four chemotherapies. None of them responded to any of those interventions.

DR. NERENSTONE: I just have one question again for really our lymphoma experts. My concern is because we have so little prolonged efficacy data in terms of time to progression or the standard that we do use, which is

survival, I have no problems with this in the Rituxan-refractory patients. My questions is when this gets out into the community, it will be another option for physicians to choose instead of Rituxan. We have some data that if they fail Rituxan, they can get the new monoclonal and have a decent response rate. We don't know, once they fail the new monoclonal, if they can cross over to Rituxan. There's no data about that. So, in fact, there's a possibility that you could actually be decreasing survival. We've been told by the lymphoma experts who gave the drug that we know that these patients get multiple sequential treatments.

Again, I have no question that it's an active agent. We don't know yet where in the queue it belongs. Is that something that we should be worried about in terms of approval?

DR. KEEGAN: I think that's why we asked the question. We think that it's something that really needs to be discussed where it stands in the queue and whether or not this should be available as an alternative to Rituxan as performed in the 04 trial.

DR. NERENSTONE: What about the lymphoma consultant?

DR. LEVINE: It's a rough question. I don't know the right answer, to be honest with you. The response

rate in the patients who had failed Rituxan was 60 percent. They've not been looked at head to head, but it looks like it's a little bit less, in fact, in the patients who were treated with the Zevalin alone, i.e., who have not had Rituxan before. There the response rates were 70, 74, whatever it was, a little bit less.

I don't think it would be wrong to ask for Rituxan first. The big issue to me is the long-term radioactivity and the long-term toxicity to the bone marrow and the myelodysplasia. That would be the conservative approach. I wouldn't be upset by that kind of approach. It's probably what would be done in the community in a general sense.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: I would agree. No one has any illusions about curing these patients, and I think the idea is to afford minimal intrusion onto lifestyle and minimal risk of toxicity. So, my own view of the queue is that this would be used, at least from the data we have, after Rituxan failure as its most obvious point of potential benefit.

Now, we obviously can't legislate that. Once it's out in the community, people are going to have their ideas about this. Again, that's part of the product labeling and part of how it's ultimately marketed.

DR. NERENSTONE: Well, actually the application is not for only in Rituxan-refractory patients. So, the application is really in previously treated.

DR. SAUSVILLE: Right. And the questions make a distinction here. We will have the opportunity to convey varying enthusiasm, I think, when we answer the questions.

DR. NERENSTONE: If there are no further comments, then why don't we get to the questions.

In the two clinical trials, the Zevalin therapy was associated with durable objective tumor responses, as well as a high proportion of severe and life-threatening hematologic toxicity of prolonged duration. Zevalin is a combination of both Rituxan and a radiolabeled monoclonal. Approval for this product requires demonstration that both components contribute to benefit and, therefore, there should be a determination that Zevalin provides benefits beyond those provided by the Rituxan alone.

In the setting of treating chemotherapy and Rituxan-refractory patients -- so, this is really now specifically the Rituxan-refractory patients -- do the data support a determination that the clinical benefits associated with Zevalin extend beyond those that could have been realized by retreatment with Rituxan?

I think the comments have been yes. Any further? Do you want a vote? Can we have hands up, hands

down, or do you want a count? We have a count now.

So, 1a, does the data say that the clinical benefits with Zevalin extend beyond those that could have been realized by retreatment with Rituxan? We need to go around the room. Dr. Sledge?

DR. SLEDGE: Yes.

DR. NERENSTONE: Everyone is voting, including our consultants, except for Mr. Ohye.

DR. BRIDGES: Dr. Bridges, yes.

DR. REDMAN: Yes.

DR. TAYLOR: Yes.

DR. PELUSI: Yes.

MS. KRIVACIC: Yes.

DR. GEORGE: Yes.

DR. BLAYNEY: Yes.

DR. SAUSVILLE: Yes.

DR. NERENSTONE: Yes.

DR. LIPPMAN: Yes.

DR. LEVINE: Yes.

DR. PRZEPIORKA: Yes.

DR. KELSEN: Yes.

DR. CARPENTER: Yes.

DR. NERENSTONE: We haven't had a unanimous vote in two days.

Do the benefits associated with Zevalin use,

clinically significant tumor shrinkage, considered together with the toxicity, both hematologic and other, support a determination that Zevalin is safe and effective in this setting? Again, we're talking about the Rituxan-refractory patients.

Dr. Sledge?

DR. SLEDGE: Yes.

DR. BRIDGES: Yes.

DR. REDMAN: Yes.

DR. TAYLOR: Yes.

DR. PELUSI: Yes.

MS. KRIVACIC: Yes.

DR. GEORGE: Yes.

DR. BLAYNEY: Yes.

DR. SAUSVILLE: Yes.

DR. NERENSTONE: Yes.

DR. LIPPMAN: Yes.

DR. LEVINE: Yes.

DR. PRZEPIORKA: Yes.

DR. KELSEN: Yes.

DR. CARPENTER: Yes.

DR. NERENSTONE: In patients who have not failed Rituxan, has Zevalin been demonstrated to provide benefits beyond those attributable to Rituxan alone? And I'll make things difficult. I'll start with Dr. Carpenter.

Any comments? If you want to vote and add comments at that time, feel free to do that. Dr. Carpenter?

DR. CARPENTER: Yes.

DR. KELSEN: Yes.

DR. PRZEPIORKA: Yes.

DR. LEVINE: Yes.

DR. LIPPMAN: Yes.

DR. NERENSTONE: I'm going to abstain.

DR. SAUSVILLE: No.

DR. BLAYNEY: No.

DR. GEORGE: No.

MS. KRIVACIC: No.

DR. PELUSI: No.

DR. TAYLOR: Yes.

DR. REDMAN: Yes.

DR. BRIDGES: Yes.

DR. SLEDGE: No.

DR. NERENSTONE: I'm going to change mine to a no.

The question we just voted, has Zevalin been demonstrated to provide benefits beyond those attributable to Rituxan alone in patients who have not failed Rituxan.

DR. ALBAIN: No.

DR. NERENSTONE: The vote is 8 to 8, 8 yes, 8 no.

Again, in patients who have not failed Rituxan, is the net clinical benefit of Zevalin, as compared with Rituxan, higher overall response rate, absence of a clear difference on time to progression or overall survival and higher toxicity, sufficient to recommend approval for this patient population?

Dr. Przepiorka?

DR. PRZEPIORKA: Just to clarify, is this full approval?

DR. NERENSTONE: Right now we have before us full approval.

Dr. Carpenter, would you like to start again?

DR. CARPENTER: Let me think about this one for a minute.

DR. NERENSTONE: Abstain.

DR. KELSEN: Yes.

DR. PRZEPIORKA: No.

DR. LEVINE: No.

DR. LIPPMAN: No.

DR. ALBAIN: No.

DR. NERENSTONE: No.

DR. SAUSVILLE: No.

DR. BLAYNEY: Yes.

DR. GEORGE: No.

MS. KRIVACIC: No.

DR. PELUSI: No.

DR. TAYLOR: Yes.

DR. REDMAN: Yes.

DR. BRIDGES: Yes.

DR. SLEDGE: No.

DR. CARPENTER: Yes.

DR. KEEGAN: Dr. Nerenstone.

DR. NERENSTONE: Yes.

DR. KEEGAN: Since the committee has not recommended I guess under 2b approval for this indication --

DR. NERENSTONE: Well, let me just read the final count. Yes, 6; no, 10.

Now your question?

DR. KEEGAN: The only study in which patients with IWF A or transformed were studied was in the randomized controlled trial. So, we wouldn't need any votes but just some general discussion on this area, in particular, additional studies.

DR. NERENSTONE: In terms of the third question? The question, as written, is in the randomized, active controlled study, 106-04, which is what we decided wasn't enough for full approval, a small number of subjects with low-grade nonfollicular non-Hodgkin's lymphoma or CD20 positive lymphoma that had undergone transformation to a

more aggressive histology were enrolled. The clinical behavior and level of CD20 expression in low-grade nonfollicular lymphoma and low-grade lymphoma that has undergone transformation may be sufficiently different from that observed in low-grade follicular non-Hodgkin's lymphoma to preclude extrapolation of the clinical results. The data obtained in these subgroups across other studies have not been as rigorously confirmed for histologic diagnosis or documentation of tumor response and duration.

There's the table that we've reviewed.

And it goes on to say that the Rituxan is approved for the treatment of chemo-refractory low-grade nonfollicular non-Hodgkin's lymphoma, the IWF A group. Although the data for Zevalin in this group are quite limited, the response rate was high, duration of response was similar for the patients who received Zevalin as compared to those who received Rituxan.

Please discuss whether the data are sufficient to determine that Zevalin has benefits beyond those of Rituxan and there's a net clinical benefit of Zevalin for chemotherapy-refractory low-grade nonfollicular NHL. In particular -- and I think this is really your question -- does this subpopulation require independent data, or can we lump them all together with the limited number of patients with IWF A to support a determination regarding the IWF A

patients?

And if the data are insufficient, discuss the design of additional studies that would be acceptable.

DR. SIEGEL: I guess as Dr. Keegan was pointing out, this question is substantially different given the advice regarding the front-line trial. It should be pointed out, if it's not clear to this committee, that the trial for use in Rituxan-refractory patients specifically excluded patients with transformed or IWF A. So, it was only for follicular. So, if we were to approve in refractory -- well, the way the questions are worded is perhaps not targeting that particular, but if there's a feeling as to whether they should or shouldn't be together, more guidance on that I think would be useful.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: The approach that was taken here to stratify them is, in general, an appropriate one. I think the issue is whether or not you want to have additional understanding of the subgroup as a disease and consider that in relation to what you see. This is where, quite frankly, I think our database is a little bit less secure about the magnitude and intensity of CD20 expression. They clearly should be broken out as a separate group.

I think that in subsequent studies attention to

the efficacy of the targeting is going to be key in understanding the true level of efficacy of this agent in comparison to the other. And that's how I would do it.

DR. NERENSTONE: I guess my response would be, because you're going to get into the transformed patients as well, that in that subgroup of patients looking at a phase II study with a response rate would be sufficient if this monoclonal antibody in other subtypes where you have many more patients available for study where there is a linkage between response rate and clinical efficacy and benefit endpoints, you don't need to redo a whole phase III, but a phase II with sufficient numbers to get a response rate would be a compelling supportive document to allow a broader indication.

DR. SIEGEL: I don't know that we could consider actually an indication for transformed NHL in patients who failed Rituxan since we haven't approved Rituxan for transformed NHL.

DR. NERENSTONE: No. I'm saying if there are other studies that you get a first indication, then I think a supplement looking at just those patients in a phase II would be appropriate. You don't have to do a large phase III. That would be a supporting indication.

DR. SAUSVILLE: Actually to elaborate on that, you could make the entry criteria for the phase II whatever

you want in terms of prior Rituxan treatment.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: The other concern that I have is if we start saying yes to follicular and no to IWF group A, we may end up having to do this for a lot of other protocols with hematologic malignancies coming down the line. And since we treat them fairly similarly and we haven't proved that this treatment is different and we don't have an expectation that it would since they are both low-grade and CD20 positive, so the mechanism of action shouldn't be different between the two groups, and more importantly, they're a very small percentage, which will give you an idea of whether or not you'd be able to actually do a study within a reasonable period of time, I would suggest not having to do something different about that particular group.

DR. NERENSTONE: How do you feel about the transformed patients?

DR. PRZEPIORKA: Oh, those are a completely different group, and I don't know that you can make any conclusion from this data. I would agree that it's nonconclusive, and I was surprised to see it in here at all.

DR. NERENSTONE: Dr. Levine.

DR. LEVINE: I would agree. It seems very

reasonable to me to include the IWF A patients in with the follicular patients in this application and would feel very different about the transformed.

DR. NERENSTONE: Yes, Dr. Redman.

DR. REDMAN: Not as a lymphoma expert, but as a clinical trialist, at a previous meeting or two meetings back, we had a trial that was totally negative and the industry was trying to support a stratified arm as being positive specifically for that group. I really look at this as the converse. If it wasn't decided beforehand, they stratified to make sure the risk factors were equal in all arms, and the majority felt that it shouldn't be approved for this indication. But if we had approved it and then gone and nitpicked on subgroups, I don't think that's appropriate the way the trial was originally designed.

Bowing to the lymphoma experts, if that's a problem, then the trial should have been designed differently, but this is the way it was designed and this is with the approval of the FDA.

DR. NERENSTONE: Dr. Lippman.

DR. LIPPMAN: Yes. That was exactly my point. You indicated it much more eloquently than I did. I don't treat these patients as a head and neck doctor. The issue is as a clinical trialist I have a concern with designing a

study to answer a question and then pulling out a small subgroup of patients and saying they're different. That should be something that's indicated a priori.

DR. NERENSTONE: Dr. George.

DR. GEORGE: Just to add one more time something to this point. Let's be clear about what the stratification does in clinical trials. The reason you do stratification is to have balance and to provide for a little more efficiency in the overall test. It is not generally to answer the question separately in each stratum. That is explicitly not the purpose. And I think we do get into trouble if we, after the fact, start looking at it as one of the purposes and say, well, we stratified it, so we should be looking at these results. Most likely we shouldn't even be doing anything like computing a p value within each of the stratum. Really, it's the overall that counts. You can look at differences as sort of some information, but it's not a generally acceptable thing to do.

DR. NERENSTONE: Did the FDA get enough sense of the committee?

Can we go onto number 4? Do we need to go on to number 4? Pat, do we need to go on to 4?

DR. KEEGAN: Yes.

DR. NERENSTONE: All right. The initial step,

the step 1 administration of the Rituxan and the indium-labeled monoclonal, is an essential component of the therapy. There are no data on the safety and effectiveness of the Zevalin using only one dose of Rituxan, the elimination of step 1, and an inadequate safety database in patients who received Rituxan alone without radiolabeled material in step 1.

They're worried about the patients who have preexisting anti-murine antibody and that might be different than that observed in clinical studies. No other screening, i.e., HAMA, has been adequately evaluated to identify patients at increased risk of altered biodistribution.

Then they're also worried about alterations of clearance for mechanical reasons or based on tumor proximity and that may provide information on radiation dosimetry to assist in assessing cumulative doses for future planned radiotherapy.

The agency seeks advice on the additional post-marketing studies to better assess the utility of using indium-labeled monoclonal for determination of biodistribution, as a component of step 1, in optimizing the safety and effectiveness of the Zevalin. What types of studies and other data should be collected to determine the safety and effectiveness of deletion of the biodistribution

assessment while retaining the first dose of Rituxan?

Dr. Przepiorka.

DR. PRZEPIORKA: I think the first step that's necessary in order to answer any questions that we could possibly ask about this is do we have the software to accurately measure what we want to measure. I think my sense from Dr. Meredith's presentation is we don't have that available. So, unfortunately, I would not be able to say yes or no or what to do without knowing what it is that we can do or what it is that we actually have done, since all of our correlations between the dosimetry and toxicities were based on possibly faulty calculations.

DR. KEEGAN: Dr. Przepiorka, could I clarify that there are two different things you could do with this initial step in the imaging. The first is a rather qualitative imaging assessment which requires no software other than the radiologic film and a radiologist to be looking at it and to get a general assessment. I think we were focusing somewhat on that more than on the dosimetry question because we would agree with you that the dosimetry is really not well developed enough to make very accurate predictions about the dosimetry with this type of a radiation source.

But we were also concerned about the issue that there are qualitative differences that can be detected on

imaging. For instance, the outlet obstruction issue that we mentioned is quite frequently detected on other kinds of scanning that we see commonly where it's just an imaging study, and it could also be seen here where it might be predictive or a gross alteration in biodistribution which might be indicative of some alteration in clearance which may or may not be immune mediated. I don't think we have a good understanding of all of that.

So, if you could separate out the dosimetry issue even from just a gross biodistribution assessment in your response, that would be helpful as well.

DR. NERENSTONE: I just have one question. Everybody keeps getting back to urinary obstruction. For clinically significant urinary obstruction, for those of us who use cisplatin all the time, there's a much cheaper way of doing it than a radioisotope scan, and that's called a creatinine. Is there an indication that the creatinine may be normal but the biodistribution may be altered when it's just an obstruction with normal creatinine?

DR. MILLS: Part of the issue comes from, one, the kidneys are very sensitive in this system in terms of the radiation effect that you may elicit, and if you get slow clearance or incomplete clearance from the kidneys, number one, that's a sensitive organ.

Number two is we have also with other

radionuclides just recently demonstrated significant problems with the bladder, and hemorrhagic cystitis has been another occurrence.

So, while your creatinine may not be affected necessarily, the residence time within these other organ structures may preclude safe distribution. So, if we have an image study that we're already performing at the present time, the biodistribution, it's another sensitive indicator, not necessary to add an additional type of evaluation. And then you may have other evidence such as evaluation of the adequacy of the preparation of the dose. That's another element that could be also assessed.

But the other concern, of course, is to know where the distribution of the tumor sites that are localized where the radiation oncologist may have additional information or understanding or want to be able to understand further where there should be applicable concerns in terms of their treatment fields too.

DR. NERENSTONE: So, do you foresee then the indium imaging as always being needed because many of these patients are going to go on to subsequent radiation therapy?

DR. MILLS: Too broad of a question. I think when we start out with this limited data set, my concern is to gather information for the various community hospital

settings. However, I could imagine that you will find subgroups in the future, especially because you have other imaging modalities where you may know the distribution of the tumor, we may have assessed that some of these safety concerns have been able to be relieved with a broader experience. So, I wouldn't say forever, but my concern is that there may be patient populations that you will see in the clinical setting that you may never leave biodistribution imaging; other groups that you may say, no, this group is safe in terms of being able to evaluate them. We just don't have that body of evidence to have that confidence yet.

DR. NERENSTONE: Dr. Sausville.

DR. SAUSVILLE: I guess the question, as asked, is a fairly open ended one. There's obviously, from the research standpoint, lots of interesting things that you could think about doing here. Could maybe you elaborate on what you would regard as easily obtained parameters with what you are likely to have in hand and how these might, in the agency's mind, have an impact in defining the further use of this?

DR. KEEGAN: I think our concern, because I'm not sure, as you say, the imaging is the only way to identify outlet obstruction, that there might be other modalities. But in particular, I think we don't feel that

we have truly assessed in an adequate population what might be the incidence of abnormal biodistribution that would suggest that the product is not going to go where it's intended and that it would be inappropriate to administer it.

That gets back again to the question. If the incidence of that happening in a particular well-selected patient population was less than a certain amount, we could collect data up until we have an adequate experience to exclude that altered biodistribution doesn't happen in more than .5 percent or .2 percent or .002 percent of the population who might be inappropriately treated if the committee felt that way.

So, I guess what we're asking is, is there some level of safety data or incidence of an adverse event that would be so uncommon -- in this instance, altered biodistribution -- that you don't think that it would be necessary to prescreen patients to look for it?

DR. SAUSVILLE: But the interesting question that you raised is do we know what a normal distribution is and how do we get that.

DR. KEEGAN: Again, this is based on our experience with monoclonal agents to date. Our thought is that there is a fairly clear pattern of normal distribution and when there has been evidence of an immune response,

that the biodistribution is so drastically altered that it's a fairly gross finding and fairly easy to detect. So, we think that normal biodistribution can be described and abnormal biodistribution can be described.

DR. SAUSVILLE: I think everyone would support the idea of continued data to address this point because, as was pointed out, if you could eliminate it, I think it would be a lot easier to use, recognizing that you still might need to determine what the role of the two versus one addition of rituximab in the regimen is. On the other hand, if you can define subsets in which it would be the bellwether of either success or failure, that would be equally important.

DR. KEEGAN: Is there a particular incidence of abnormal biodistribution that would likely preclude efficacy that you would find acceptable to miss, not to seek, through an imaging evaluation or through a biodistribution evaluation?

DR. NERENSTONE: Well, given that this is going to be a concern of more than this one application, my suggestion was that you convene a panel of imaging experts who are used to looking at dosimetry because I think it's probably not something that most of the medical oncologists are very comfortable talking about, setting limits in future studies. I think it's a good question and an

important one, but I'm not sure this forum is the right place to address it.

DR. SIEGEL: These studies can address the extent to which this early biodistribution study will generate information that might impact whether the patient is treated or what concerns there are, safety or efficacy-wise.

But one of the things it won't address -- and I wonder if there's some insight -- is whether it will provide useful information about future management of the patient with external beam radiation. I don't even want to go with future radiation therapies that don't now exist, but with future external beam radiation. Is this a population that has a significant probability of later receiving external beam radiation, and if so, would the information from where this drug dosed the patient be useful in planning and designing that later radiation?

DR. NERENSTONE: Dr. Bridges, you're a radiation therapist.

DR. BRIDGES: Yes. I think it's a very important point. I expect that if this is approved, there will be a push in the community, and I'd ask the medical oncologists if there would be use of this prior to potential radiation therapy and that radiation would highly be likely to come on later at a point in the course of the

patient's care. Because the response rate with radiation to a lymphoma mass is approaching 90 percent, so it's really the best single agent we have. But many times we reserve it for later use because we want to get the systemic problem taken care of.

So, I think it's going to be important to be able to identify the dosimetry issues related to the critical structures like particularly spinal cord, kidney, and things like that. So, I think it's going to be paramount that we do get more dose analysis done.

There's got to be a clarification to the medical oncology community somehow that this is an issue, that when you get a patient, you've got to, in your review of systems, ask have you had this treatment. I mean, obviously we do. And then it's got to be something that's in the package insert, that there's a big, bold precaution, and it's got to be communicated, even at our national meeting level, to make sure that this is an issue for us. Because it's not been raised before significantly, as far as I know, in the community.

DR. SIEGEL: Would you anticipate then, if you had a patient that you were going to give external beam to who had previously received this product, that you would or might want to go back and look at the indium imaging to see where the radiation from --

DR. BRIDGES: Clearly, the data you provided today -- if the patient had a paraspinal mass with a cord compression and I had the risk that he had already gotten 8,000 rads to the superficial spinal cord and now I'm contemplating 4,000, 5,000 more, it would be very important for me to know. The concern I would have -- if people are aware of it, they're going to look and they're going to get the indium study. They're going to look at it. They're going to verify where the tumor mass was, but if they're not aware of it, it's not something that we normally think about in consideration of radiation after other radioactive treatments.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: To get back to the biodistribution question, I think this is going to be tedious enough to use for medical oncologists that it will generate substantial pressure on the company to perhaps come to you and present their data. And for us to pose a hypothetical 2 percent or some number at this point, based on limited experience, I think is asking too much. So, my advice would be to keep an open mind, and if there's a subset that this sponsor or other sponsors can identify where it's no issue, then you might want to go ahead and approve abandoning the imaging dose.

DR. NERENSTONE: But I think someone has to be

keeping a record of what's going on because we're going to be out in the community and those people who give it are going to give it, and then they go on and they get it. And if nobody is looking at these results in a centralized way, we're not going to have any idea at the end of the day what we're doing there.

Dr. Sledge.

DR. SLEDGE: In contrast, I've got to ask. You've treated close to 500 patients, according to the sponsor, and the biodistribution issue basically hasn't been an issue in those 500 patients. Let me ask the agency what reasonable trip wire is going to be required if you've already got data on 500 patients. 2,500, 25,000? How many more do you think you need?

DR. KEEGAN: Well, in fact, we don't have dosimetry information on close to 500 patients. It's more on the order of low 200's. Right?

DR. SLEDGE: No, but that's what you have safety data on, 500 patients. It's reasonable to suggest that this has not been a major problem to date with 500 patients.

DR. KEEGAN: I guess our concern is that alteration of the biodistribution may alter both the safety and efficacy profile, safety we may not have seen or may not have observed, particularly if it was just one person

or two people. I guess what it goes down to, if we have a sufficient number, if we conclude that this might occur in less than 1 percent of the population, again --

DR. SLEDGE: Don't you think you're already pretty close to being there?

DR. KEEGAN: We may be close to being there. We don't have the correlative biodistribution data except for about 200 folks, though. So, we're not quite at the 1 percent rate.

DR. SLEDGE: From a kidney, ureter, bladder standpoint, this certainly seems safer than cisplatinum, for instance.

DR. SIEGEL: I guess there are a couple other differences between use in clinical trials and use in practice that have come up in our discussion. These patients were screened for lack of anti-murine antibodies. It has not been proposed that that screening be done, but one could study whether such screening would be a reasonable alternate. We know from, at least other products, that such antibodies can cause radical changes in the distribution of labeled antibody. I assume there were other screening parameters regarding kidney function and other factors that may or may not be applied the same way in the community.

But I guess the reason I asked that other